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EXPERIMENTAL STUDY ON REGENERATION OF THE URINARY BLADDER

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EXPERIMENTAL STUDY ON REGENERATION OF THE URINARY BLADDER

by

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I. INTRODUCTION

In the present surgery, methods which are used in making a substitute bladder following total cystectomy, consist of 4 types as follows:

- A) External ureterostomy,
 - B) Ureterosigmoidostomy,
 - C) One in which the intestine is used as a urinary reservoir and
 - D) Regeneration of the urinary bladder.
- A) External ureterostomy has advantageous points that it has no operative

risk and sometimes it is possible to wash the renal pelves, but it has an inconvenience to have to carry always urinals (Rutzen bag) and a danger of having ascending infection.

B) In ureterosigmoidostomy using a segment of the intestine as a substitute bladder, there are brought about unbalance of blood electrolytes and a danger of ascending infection, especially in case of ureterosigmoidostomy, because there is non-physiological condition that urine is introduced into an intestinal segment which is originally an organ for absorption, and this fact results in making of hyperchloremic acidosis. In order to prevent those serious complications, BRICKER (1950) tried to construct the ileal bladder upon 55 patients and reported that intestinal reabsorption of urine was less than in cases of ureterosigmoidostomy, hyperchloremic acidosis being prevented.

C) In ureteroileostomy, the ileum is utilized as a substitute bladder following total cystectomy. When an isolated ileum segment is used merely as a conduit of urine, there is no change in blood electrolytes, but when it is used as a reservoir, there is reabsorption of urinary elements, especially of chloride, resulting in unbalance of blood electrolytes. In order to prevent these complications, SHOEMAKER (1955) tried to establish a procedure to prevent hyperchloremic acidosis by using inverted seromuscular graft.

D) Regeneration of the Urinary Bladder. As mentioned above, many authors dared to use the intestine or the bowel as a substitute bladder, though they were conscious of many faults in the method. There are, however, few reports about regeneration of the bladder. Once, TIZZONI and FOGGI (1888) reported that after ureteroileovesical anastomosis, the ileal bladder had changed to a little diverticulum and the remnant bladder had further enlarged, regenerated and deformed into a perfect bladder. SCHWARTZ (1891) performed cystectomy preserving the trigone, and implanted the ureters to proximal of the urethra, expecting regeneration of the urinary tract derived from the urethra. NEUHOF (1917) transplanted femoral fascial graft to the site of cystectomy and proved proliferation of the uroepithelium. PHEMISTER (1923) and KOOTZ (1929) made supplementary experiments of this procedure. SCHILLER (1923), using rabbits, experimented regeneration of the bladder following cystectomy preserving the trigone. And he reported about each of three layers, that is, uroepithelium, connective tissue and smooth muscle. RAVASINI (1925) reported a clinical case of a tumor involving the entire bladder except the left half of the trigone and a small portion of the adjoining wall. He resected the entire bladder except this area: the right ureter was reimplanted into a healthy part and sutured to the cut margin of the trigone. The cystogram after 8 weeks showed formation of the new bladder. This experiment was followed by PERLAMMAN (1927), who insisted that the urinary bladder could be regenerated from the urethra. KRETSCHMER and BARKER (1928) performed the SCHILLER's method upon dogs, but failed to obtain the regenerated bladder. FOLSOM (1940) performed also the Schiller's method on 8 patients of cystitis and reported that he had succeeded clinically. SISK and NEU (1939) performed cystectomy upon a patient with bladder cancer: he

reported that, in 5 months and a half after operation, the patient urinated at intervals of 2 to 4 hours and the capacity of the new bladder was 3 to 4 ounces. RICHARDSON (1952) reported cases of total cystectomy excluding the bladder neck: after a year and a half, the regenerated bladder was 350 cc in capacity, and he emphasized that the bladder had strong regenerating activity. DEMUTH and MURPHY (1953) performed cystectomy on dogs and transplanted an inverted fascial graft, which was isolated from the anterior rectus sheath, to the site of cystectomy, where uroepithelium proliferated and a new bladder was regenerated. DRAPER (1952) reported a case in which after cystectomy, a skin graft was transplanted to the site of cystectomy and hair grew at the place. GARRET (1954) reported regeneration of the new bladder from a small healthy portion left behind following resection of total necrotized bladder caused by arterial thrombus. BOHNE and OSBORN (1955) reported regeneration of a new bladder after total cystectomy, together with the regeneration of smooth muscle on the regenerated bladder wall. They performed cystectomy excluding a small portion of the dome and implanted ureters into the portion: thus, after 3 postoperative years, the cystogram showed a normal shadow of the regeneration of a new bladder of 350 cc in capacity, and the patient urinated under a usual pose.

The above mentioned are the reports published till my experimental survey was begun: and all of them pointed out the fact that the bladder has an active regenerative ability. Encouraged by these reports, I have made effort to regenerate a new bladder following total cystectomy and the following experiment have been tried.

EXPERIMENTAL WORK

(1) MATERIALS AND METHODS

Twenty-two dogs were used for this experiment. Five dogs died of surgery directly, the remaining seventeen survived and were investigated for complete evaluation.

As experimental animals, adult female mongrel dogs with 7.5-15 kg of body weight were used. After being anesthetized with Auropan-soda solution, the dog was fixed on the table in supine position. Then, after suprapubic midline incision was made, the ureters were identified, the small intestine being expelled upwards: the right ureter presented peristaltic movement, closely adhering to the posterior wall of retroperitoneum and the left one was a little difficult to identify. The ureters were dissected about 10 cm proximal from the bladder and holding sutures were placed at the stumps.

(i) Insertion of the Mold (Fig. 1):

After exposure of the ureters, the perivesical fatty tissue on the anterior wall of the bladder was either sharply or bluntly dissected from the parietal peritoneum, by ligating the cranial and caudal vesicular arteries and cutting the urethra: thus total cystectomy was finished.

Next a mold was inserted into the space from where the bladder was removed. The mold is to be connected previously with ureterourethral catheters. The ureteral

catheters were at first introduced into the ureters retrogradely; in this process of the operation, a palpation was necessary to guide the ends of the catheters correctly, so that they could reach the renal pelvis properly. Then the urethral catheter was introduced into the urethra from the internal orifice and was fixed to the greater labium, preventing urethral catheter to slip off owing to the peristalsis. The holders which had been sutured to both ends of the ureters were tied with perivesical tissue to fix the mold. Then the mold was covered closely with the perivesical fatty tissue, and peritonealization was performed with continuous or interrupted sutures. In this process, as the dog's ureters are very slender, it was very difficult to insert the ureteral catheter retrogradely into the renal pelvis, and the ureteral catheters were liable to be bent near the mold.

In 3rd to 8th postoperative week, the mold was removed through an incision of about 3.0 cm on the anterior wall, to observe the condition of adhesion between the parietal peritoneum and the pouch. In general, the wall of the pouch was 0.8 to 1.0 cm in thickness after 10 postoperative days: the inside of the wall was smooth, and urine was noticed to spring out from the ureteral orifices. An anastomosis between ureters and the regenerated bladder was almost completed in this period. Then the urethral catheter was inserted into the urethra and was fixed to the external urethral orifice: this catheter was drawn out in general a week later, from the external urethral orifice. When the pouch was closed, cares had to be taken so that silk thread would never come out to the inside of the wall. Immediately after the operation, 1.0 g of streptomycin and 200,000 units of penicillin were sprinkled into the cavity, and for 3 postoperative days, intramuscular injection of 1.0 g of streptomycin and 200,000 units of penicillin and intravenous injection of 100 cc of 5% glucose solution were given every day, which were continued further according to the condition of the animal.

(ii) Kinds and Shapes of the Mold:

The mold was used to form the shape of a urinary bladder extraperitoneally. Two kinds of mold were used: one was a resin mold and the other a polyvinyl formal mold (Figs. 2 and 3). A resin mold was made in the following way:

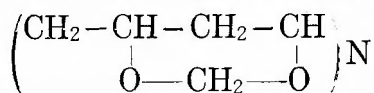
1. At first, a positive primary model was made of paraffin.
2. The paraffin model was buried into gyps, which was left to be hardened itself.
3. Paraffin was removed with hot water, and the negative gyps model was obtained.
4. Mixture of resin powder was put into a metal cap.
5. Both parts of the cap were bolted up so tightly that they might unit closely together.
6. They were taken out of the boiled water of 100°C and left to be cooled in the room temperature; and they were joined together with Mend-Rex.
7. After being polished with a grinding machine, two holes for insertion of ureteral catheters were made with bar on both side of the mold, and one for a urethral catheter in the caudal portion. When the catheters were inserted into these

holes, they were fixed with Mend-Rex.

This resin mold was disinfected with 0.1% Osvan solution.

The other mold, i. e. a polyvinyl formal mold, was made of polyvinyl alcohol formalized through action of formalin. Its chemical structure is as follows (Fig. 4).

Fig. 4 Chemical Structure of Polyvinyl Formal.



Specific characteristics of polyvinyl formal are as follows:

1) It is originally white and spongy, but when it is soaked in water, it becomes soft and flexible. Furthermore, when it is indwelt in the vital body tissue for a long time, it is absorbed gradually and diminished completely.

2) Irritation by the substance itself upon the vital tissue is comparatively slight.

This mold was made in the following way: A suitable size of its mass was cut off with a sharp knife and then three holes were made for ureteral and urethral catheters. These catheters were fixed to the mold owing to elasticity of polyvinyl formal itself. The disinfection of the mold is easily done by boiling for 5~10 minutes. If it was pressed without refrigeration, its elasticity was reduced and its shape was deformed. In this experiment, the mold was soaked in a solution of such antibiotics as penicillin and streptomycin, before it was used for operation.

As for the shape of a mold, two kinds were applied; one was the mold, on the dome of which ureteral catheters were inserted, and in the other the ureteral catheters were inserted into the middle of its posterior wall. When the former was used, it had a disadvantage that the ureteral catheter was liable to be bent at its joint when it was inserted into the ureter. The latter was used to avoid this disadvantage; that is, it was devised to take a shape with as close a resemblance to the natural condition as possible and in fact, it was possible to prevent bending of the catheter.

(iii) On Ureteral Catheter:

It was necessary to use ureteral catheters without any harmful biological reaction or chemical stimulation, and I used a polyethylene tube of 1.27 mm in outside diameter. Disinfection of the tube could be carried out by soaking it in 0.1% Zephiran chloride, for 18 to 24 hours.

(iv) Cystometry:

Examination with cystometer was performed under general anesthesia with Auropan-soda, by SIMON's cystometer. The method of the cystometry is as follows: The dog was placed in supine position, and its bladder was emptied with a catheter. The level of the external urethral orifice was decided to be the zero-point. Internal pressure of the bladder was recorded on the paper every 10 cc of water being infused. This examination was repeated three times and the average values were calculated respectively in correspondence to the quantity of infused water. This process was tried in two ways; in one case, water was infused rapidly (110 drops per minute)

and in the other, slowly (60 drops per minute). The average value in the former showed the hypertonic curve and those in the latter, the atonic curve. Then the mean value between these 2 curves was calculated to indicate a vesicotonic curve. This cystometric examination was performed on every experimental animal postoperatively and prior to the operation as control.

(2) RESULTS

(i) Resin Mold Group:

Case 1. Dog: NO. 10. Weight 8.4 kg. Period of Survival: 14 days. Cause of Death: Urinary leakage. After total cystectomy, a resin mold with 35 cc in volume was indwelt. Urinary dribbling from the urethral catheter was comparatively much postoperatively, and there was no bloody urine, but the perineum was contaminated with urine. Though the dog squatted continually, her urination was incontinent. On 10th postoperative day, the ureteral and the urethral catheters were found to have been removed spontaneously. She had had urinary leakage and died of panperitonitis on 14th postoperative day.

Autopsy Findings: A great deal of bloody urine stagnated in the abdominal cavity; the cut end of the ureter was pulled out of the pouch and showed contractive stenosis. The right ureter was dilated markedly and formation of the pouch was incomplete; the wall of the regenerated pouch was 0.5 to 0.8 cm and its inside was rough, without proliferation of the uroepithelium. There was also stagnation of urine in the pouch. Blood electrolytes and nonprotein nitrogen had gradually increased postoperatively and they showed a marked rise on the previous day of her death.

Case 2. Dog: No. 14. Weight: 12.7 kg. Period of Survival: 7 days. Cause of Death: Urinary leakage. When a resin mold of 35 cc in volume was inserted and indwelt, after total cystectomy, the right ureteral catheter bent temporarily. Immediately after the operation, she began dribbling bloody urine. She did not recover postoperatively from surgery, and lost appetite completely and died on 7th postoperative day.

Autopsy Findings: The end of the left ureteral catheter had ruptured both the renal pelvis and the parenchyma, reaching the abdominal cavity, where a great deal of urine stagnated. Formation of the pouch was unsatisfactorily, and its wall was 0.7 cm in thickness and its inside was rough, having yellowish white slime on its surface. There was no proliferation of the uroepithelium.

The right ureteral catheter was filled with urinary elements, and the right kidney showed moderate hydronephrosis. Stink exudation stagnated in the cavity of the mold.

Case 3. Dog: No. 18. Weight: 13.0 kg. Period of Survival: 11 days. Cause of Death: Panperitonitis and pyohydronephrosis. After the total cystectomy, a 35 cc resin mold with a hole on its dome was indwelt; the dribbling urine was mixed with blood, but its urination was favorable. She did not recover from surgery completely and died on 11th postoperative day; cause of death was infection esta-

blished out of the pouch, the wall of which presented a picture of inflammatory changes and showed adhesion to the uterus and the uterine ligament on the posterior. The wall of the pouch was 0.8 to 1.0 cm and its inside was comparatively smooth, but had a slime covering. The junction between the urethra and the pouch showed no proliferation of the uroepithelium and was easily distinguished. The anastomosis between the perivesical fatty tissue and the right ureter was insufficient, and there was made an internal urinary fistula. There was stagnated purulent exudation in the mold itself.

Case 4. Dog: No. 20. Weight: 13.5 kg. Period of Survival: 21 days. Cause of Death: Strangulation. After total cystectomy, a 35 cc resin mold was indwelt. At the mid-point of its posterior wall had been inserted ureteral catheters. There was urinary dribbling from ureteral catheters immediately after the operation, and the dog recovered completely from surgery on 4th postoperative day. But as blood electrolytes were high, she was given milk mixed with a sulfa drug 3.0 g and sodium bicarbonate 3.0 g a day for 4 days. Since 18th postoperative day, her condition worsened; urinary volume decreased and the abdomen swelled severely and she died on 21st postoperative day.

Autopsy revealed that cause of her death was strangulation of the bowel, and all small intestines gathered into a mass. The anterior wall of the pouch showed a slight adhesion to the parietal peritoneum. The pouch was 35 cc in capacity; its inside was smooth and glossy and the thickness of its wall was 0.7 to 1.0 cm. When water was infused into the pouch, it was noticed to reflow into both ureters. The junction between both ureters and the pouch was comparatively sufficient, with some proliferation of the uroepithelium. Both ureteral orifices were smooth and showed no stenosis. Around the orifices, however, there was noticed proliferation of the connective tissue. There was neither hydroureter, nor hydronephrosis on each side, but the left ureteral catheter contained much urinary sediment. There was stagnation of inflammatory exudation in the cavity of the mold. Blood electrolytes and nonprotein nitrogen were recovering from postoperative elevation, showing an inclination of elevation again just before death.

Case 5. Dog: No. 21. Weight: 11.8 kg. Period of Survival: 8 days. Cause of Death: Panperitonitis. After total cystectomy, a resin mold of 35 cc in volume was also indwelt; the dog recovered from surgery in 3 postoperative days, but she began to show marked symptoms and signs of panperitonitis and died on 8th postoperative day.

Autopsy Findings: There was marked stagnation of pus in the abdominal cavity and the space of DOUGLAS's fossa, indicating the cause of death to be panperitonitis. The anterior wall of the pouch adhered to the abdominal wall and the posterior to the anterior wall of the uterus and the rectum, in such a degree as they could be dissected bluntly with fingers. The wall of the constructed pouch was inflammatory and insufficient; it was 0.7 to 1.0 cm in thickness, but presented edema on the whole and was contracted and smaller than the capacity of the mold. Its inside was covered with slime, but with rough surface, when the slime was exfoliated. There

was insufficient anastomosis between the left ureter and the pouch. The insufficiency might have developed to the urinary leakage into the peritoneal cavity.

Case 6. Dog: No. 23. Weight: 12.5 kg. Period of Survival: 41 days. Cause of Death: Pyohydronephrosis. After total cystectomy, a 35 cc resin mold was indwelt. The dog recovered well on 3rd postoperative day, and there was continuous dribbling of urine from the ureteral catheter. On 28th postoperative day, the mold was removed successfully, and formation of the pouch was satisfactory. The wall of the pouch was 0.8 to 1.0 cm in thickness and its inside was smooth and glossy; there was stenosis at the ureteral orifices, but urinary voiding was smooth. Though ureteral catheters were inserted and indwelt after the operation, urinary fistula was formed on 29th postoperative day in the scar of the operation; and urine was voided from both the catheters and the fistula. This fistula was closed spontaneously on 31st postoperative day. On 38th postoperative day, the urethral catheter was removed, and the dog's urination was good, but it was incontinent, and she would take a pose of urination at intervals of 5 to 8 minutes. She died on 41st postoperative day.

Autopsy revealed that the cause of death was ascending infection in both kidneys; the anterior wall of the pouch adhered to the parietal peritoneum, and the posterior wall, to the uterus and lig. latum. Formation of the pouch was satisfactory and its wall was 0.8 to 1.0 cm in thickness and lined with granulation smoothly. A small quantity of thick pus stagnated in the pouch. The junction between the urethra and the pouch was sufficient, being lined completely with the uroepithelium. There was proliferation of the connective tissue at both ureteral orifices and it was difficult to insert a sound on account of marked stenosis. The capacity of the pouch was 30 cc, which showed contraction due to cicatrization. Blood electrolytes and nonprotein nitrogen approached the normal level in 3rd postoperative week, beginning to rise sharply and markedly after the removal of the mold, and maintaining this state continuously till the dog died. Phenolsulfophthalein value was 48% just after the operation, but it became 12%, which indicates disfunction of the kidneys, immediately before her death.

Case 7. Dog: No. 24. Weight: 14.0 kg. Period of Survival: 16 days. Cause of Death: Peritonitis. After total cystectomy, a 35 cc resin mold was indwelt. On 2nd postoperative day, her urination was incontinent and she would take a usual pose at intervals of 3 to 5 minutes, voiding 2 to 3 drops of urine each time. Out of the ureteral catheter, however, urine was always dropping and her tail and gluteal portion were contaminated. She died on 16th postoperative day.

Autopsy revealed that the cause of death was panperitonitis due to an insufficient suture of the fatty tissue, that had wrapped up the mold. Anterior part of the pouch was especially contaminated with slime, showing marked inflammatory changes and formation of the pouch was unsatisfactory. The wall of the pouch was 0.5 cm in thickness and its inside was comparatively smooth; hydroureter and hydronephrosis were also slight on both sides. The junction between the urethra and the pouch was comparatively good, where was only a slight proliferation of the uroepithelium.

Capacity of the pouch showed slight tendency of contraction. There was purulent exudation in the mold. Blood electrolytes showed slight elevation, and nonprotein nitrogen remarkable one. As the causes for these elevations, disfunction of kidneys may be counted, but probably, deterioration owing to panperitonitis may be another one.

Case 8. Dog: No. 31. Weight: 9.5 kg. Period of Survival: 8 days. Cause of Death: Urinary leakage. After total cystectomy, a 35 cc resin mold was inserted and indwelt; when ureteral catheters were inserted, the distal ends bent, but they could be straightened by the closure of the abdomen. The dog recovered well on 3rd postoperative day, and her urination out of the ureteral catheters was good, but the perineum was contaminated with urine. Since 6th postoperative day, she began to be emaciated and died on 8th postoperative day.

Autopsy revealed that the cause of her death was urinary leakage; that is, a large quantity of bloody urine stagnated in the abdominal cavity. Formation of the pouch was comparatively good, but its inside was rough and had slime on its surface. Its wall was 0.7 to 0.8 cm in thickness, and the junction between the urethra and the pouch was distinguishable, showing no proliferation of the uroepithelium. The junction between the ureters and the pouch underwent insufficiency, and urine was guided from the kidney to the pouch only by the ureteral catheter. The right kidney had moderate pyohydronephrosis, and the left, slight one. There was stagnation of exudation in the mold.

The causes of death, complications and others of the cases mentioned above are shown in the tables Tables 1 and 2).

Table 1. Resin Mold Group

Dog No.	Weight (kg)	Volume of the Mold (cc)	The Mold with Drainage	Inserted Place of the Ureteral Catheter into the Mold	Period of Surviving (day)	Cause of Death	References
10	8.4	35	No	At the dome	14	Urinary leakage	{On 10th postoperative day, urethro-ureteral catheters were pulled out. The parenchyma of the left kidney was ruptured by an inserted ureteral catheter.
14	12.7	35	No	At the dome	7	Urinary leakage	
18	13.0	35	Yes	Middle of the posterior wall	11	Panperitonitis and Pyohydronephrosis	{On 28th postoperative day, the mold and the ureteral catheters were removed.
20	13.5	35	No	Middle of the posterior wall	21	Strangulation	
21	11.8	35	No	Middle of the posterior wall	8	Panperitonitis	
23	12.5	35	No	Middle of the posterior wall	41	Pyohydronephrosis	
24	14.0	35	Yes	Middle of the posterior wall	16	Panperitonitis	
31	9.5	35	No	Middle of the posterior wall	8	Urinary leakage	

(ii) Polyvinyl Formal Group:

In this group, the polyvinyl formal mold was applied to 11 dogs.

Case 1. Dog: No. 28. Weight: 10.5 kg. Period of Survival: 395 days. Cause of Death: Sacrificed. After total cystectomy, a 25 cc polyvinyl formal mold was placed. The dog recovered from surgery on 3rd postoperative day. Urine was continuously dropping from the urethral catheter and it took a usual pose of urination at intervals of 5 minutes. On 19th postoperative day, suprapubic incision was performed under the general anesthesia, and the mold was removed. The anterior wall of the pouch adhered to the parietal peritoneum in such a degree as they could be separated bluntly with fingers. Formation of the pouch was good, and its capacity was 25 cc, which was the same quantity as the mold. The wall was 0.8 to 1.0 cm in thickness, and the inside was smooth and glossy. The junction between the urethra and the pouch was comparatively sufficient and was lined with the uroepithelium. Both ureteral orifices were completely patent, and urine was flowing from the orifices. The ureteral catheters were inserted and the wall of the pouch was sutured serially. After the second operation, her urination was good, without forming urinary fistula. Secretory and ascending pyelogram taken on 30th postoperative day, showed that the pouch had slightly contracted. Various kinds of examinations, such as examination of renal function, determination of blood electrolytes, cystometric examination and determination of urinary quantity, were performed on 34th, 120th, 160th, 180th, 270th, 300th, 360th, 380th and 390th, postoperative days respectively. On 270th postoperative day, phenolsulfophthalein was 25%, blood chloride 408 mg/dl and nonprotein nitrogen 431 mg/dl. Examinations of renal function on the same day showed that phenolsulfophthalein was 24%, blood chloride was 406 mg/dl, approaching the normal value. Twenty four hour urinary volume was determined, and whether urination was continent or incontinent was observed. The quantity of drinking water was determined also every 6 hours. The determination was performed every hour for 24 hours after the operation, total quantity of urine in an hour being recorded. Within one month after the operation, total quantity of urine in 24 hours was 492.5 cc, and quantity of drinking water was 113 cc. Her urination was incontinent all through 24 hours. Within 3 months after the operation, total quantity of daily urine in 24 hours was 332 cc, and that of drinking water, 52.3 cc, with urinary incontinence all through 24 hours. Within 6 months, total quantity of urine was 449.0 cc and that of drinking water 218 cc, but her urination became intermittent, approaching relative continence. When she was allowed to walk freely, she squatted at intervals of 5 to 10 minutes, voiding 5 to 7 cc of urine each time. Within 10 months, total quantity of urine was 460 cc, and that of drinking water 175 cc; that is, she got rid of relative continence voiding urine voluntarily at intervals of one or two hours. In this stage, the perineum was never contaminated with urine. While allowed to walk, she used to void 50 to 60 cc urine at intervals of 40 to 60 minutes. In about 12th month, total quantity of urine was 441 cc, and that of drinking water 68 cc. She voided urine at intervals

of 2 to 6 hours, and her urination was perfectly continent. But when put to free walking, she used to void 50 to 60 cc at intervals of 40 to 60 minutes (Fig. 5).

Thus, her urination became relatively continent in about 6th postoperative month, and showed perfect continence at about 10th postoperative month, voiding urine voluntarily.

It was notable that the capacity of the bladder had enlarged 18 times as large as that of the mold, with the lapse of time. Cystometric examinations were recorded in 7th and 12th postoperative month respectively (Figs. 6 and 7). Internal pressure of the regenerated bladder was considerably hypotonic on 90th postoperative day, moderately hypotonic on 120th, orthotonic on 300th postoperative day, and slightly hypertonic on 360th postoperative day.

The vesical pressure before the operation and that of the regenerated bladder are shown in the Table 3. It is clear that the regenerated bladder changed gradually from hypotonic to hypertonic, in the lapse of time (Figs. 8 and 9). In a case of the test animals the capacity of the regenerated bladder was about 20 cc on 11th day after the removal of the mold (on 30th postoperative day), when a retrograde urogram showed reflux, ureteral dilatation, and dilatation of renal pelvis. On 380th pos-

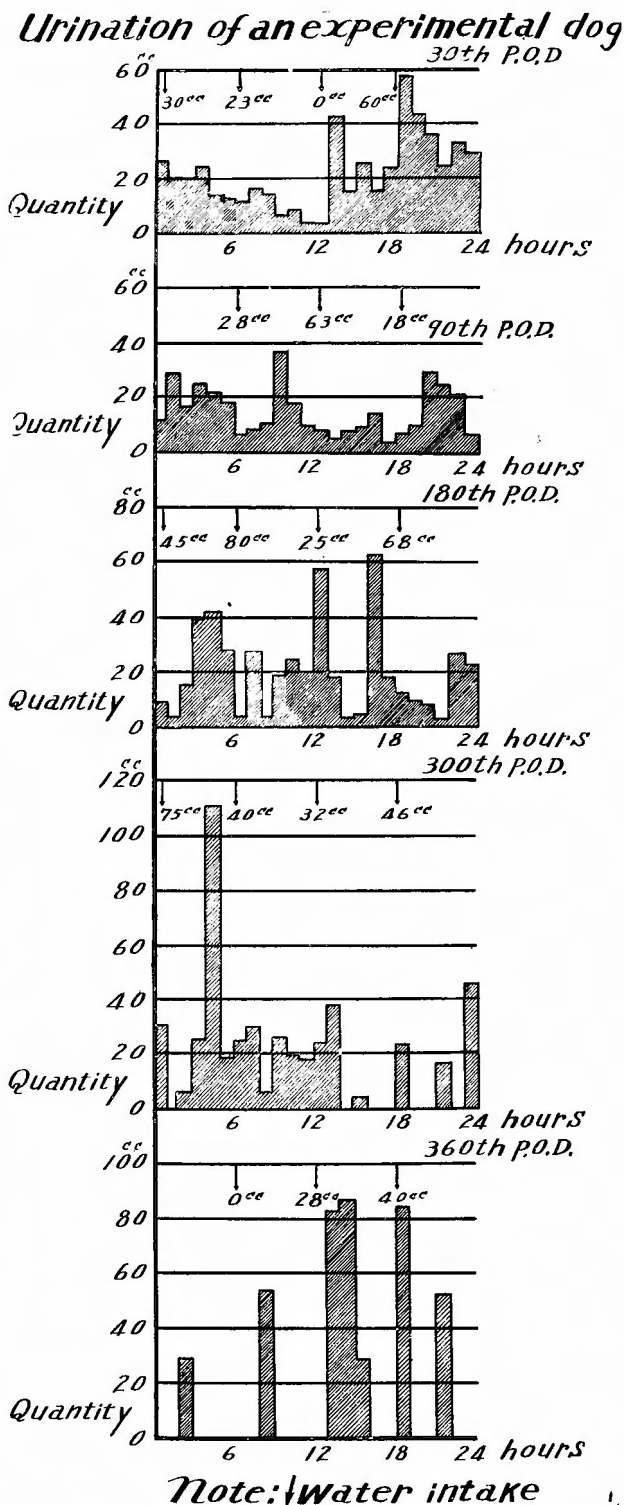


Fig. 5 The dog became relatively continent in 6th postoperative month, and then showed perfect continence in about 10th postoperative month.

Table 2. Complications of Resin Mold Group

Dog No.	Hydro-nephrosis	Pyohydronephrosis	Peritonitis	Urinary Leakage	Urinary Fistula	Slipping of Ureteral Catheters	Angulation of Ureteral Catheters	Stenosis of Ureteral Orifices	Crystallization in Ureteral Catheters	Continence	Exudation in the Mold
10	##		+	##		+		##		No	##
14	##		+	##			+		##	No	##
18	+	##	##					+		No	##
20									##	No	##
21			##	+					+	No	##
23		##			+			+		No	##
24	+		##					+		No	##
31		##		##			+	##		No	-

Note: + Slight, ## Moderate, ### Severe

toperative day, the capacity was about 45 cc, and there was also reflux and dilatation of the upper urinary tract (Figs. 10, 11, 12, 13, 14, 15 and 16). On 395th postoperative day, the animal was sacrificed with injection of Auropansoda 100mg/kg.

Autopsy revealed the followings (Fig. 20): The anterior wall of the regenerated bladder adhered slightly to the uterus and the uterine ligament, which had not formed a part of the wall themselves. The capacity of the pouch was 45 cc, which was 1.8 times as large as that of the mold. The wall of the pouch was 0.7 cm in thickness and its inside was smooth and was lined with the uroepithelium, in the lower part of which were recognized smooth muscular fibers. The junction between the urethra and the pouch was quite sufficient and indistinguishable. There was a yellowish brown ve-

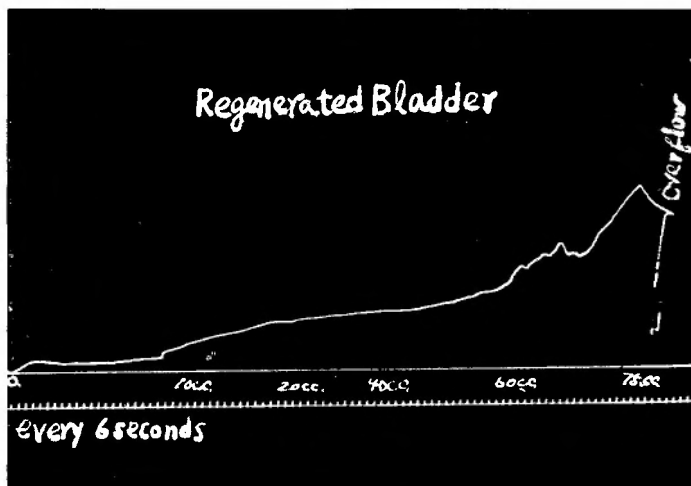
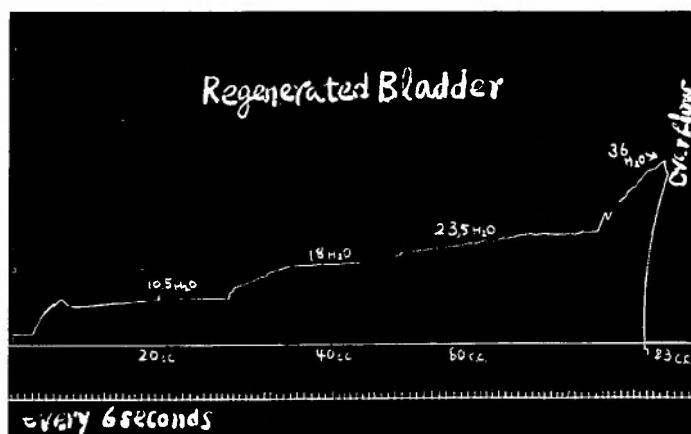
**Fig. 6** Intravesical Pressure of the Regenerated Bladder (7th Postoperative Month).**Fig. 7** Intravesical Pressure of the Regenerated Bladder (12th Postoperative Month).

Table. 3. Results of Cystometry (cm H₂O)

Volume of water infused (cc)	10	20	30	40	50	60	70	80
Postoperative day								
Before Operation	7.0	10.0	13.0	15.0	20.0	21.5	24.5	30.5
90th day	2.8	3.2	4.7	4.9	6.4			
120th day	3.5	5.1	6.8	8.0	9.0	10.5		
300th day	6.3	7.0	8.7	10.4	15.8	21.0	22.4	
360th day	9.0	15.7	22.7	25.0	27.7	30.5	32.1	34.5

sical calculus of a little-finger tip-size, 0.6 cm×0.5 cm, and there was an ossification formed in the lower part of the uroepithelium around the ureteral orifices. Both ureters and pelves showed marked dilatation. Renal parenchyma was very thin, owing to stenosis at the orifices.

Case 2. Dog: No. 29. Weight: 9.5 kg. Period of Survival: 18 days. Cause of Death: Pyohydronephrosis. After total cystectomy, a 20 cc polyvinyl formal mold was indwelt. On 11 th postoperative day, urination from the right ureteral catheter was poor, voiding bloody urine. On 13th postoperative day, the mold was removed because the dog was generally emaciated. The anterior wall of the pouch adhered to parietal peritoneum. Formation of the pouch was good; and its wall was 0.5 cm in thickness and its inside was rather rough. Junction between the urethra and the pouch was comparatively clear, and there was no development of the uroepithelium. Though it was difficult to identify ureteral orifices, there was proliferation of the connective tissue around the left ureteral orifice, which showed remarkable stenosis. After removal of the mold, a catheter was inserted retrogradely. On 2nd day after the second operation, a urinary fistula was formed in suprapubic wound, but urination through urethral catheter was comparatively good. She became emaciated gradually, without closing of the fistula and died on 18th postoperative day.

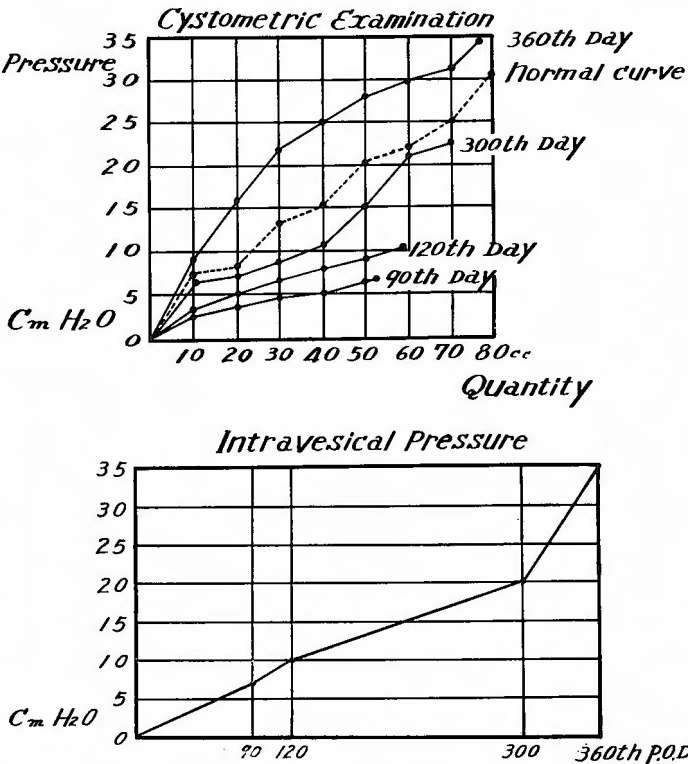


Fig. 8 and 9. It is shown clearly that the regenerated bladder gradually changed from hypotonic to hypertonic, in the lapse of time.

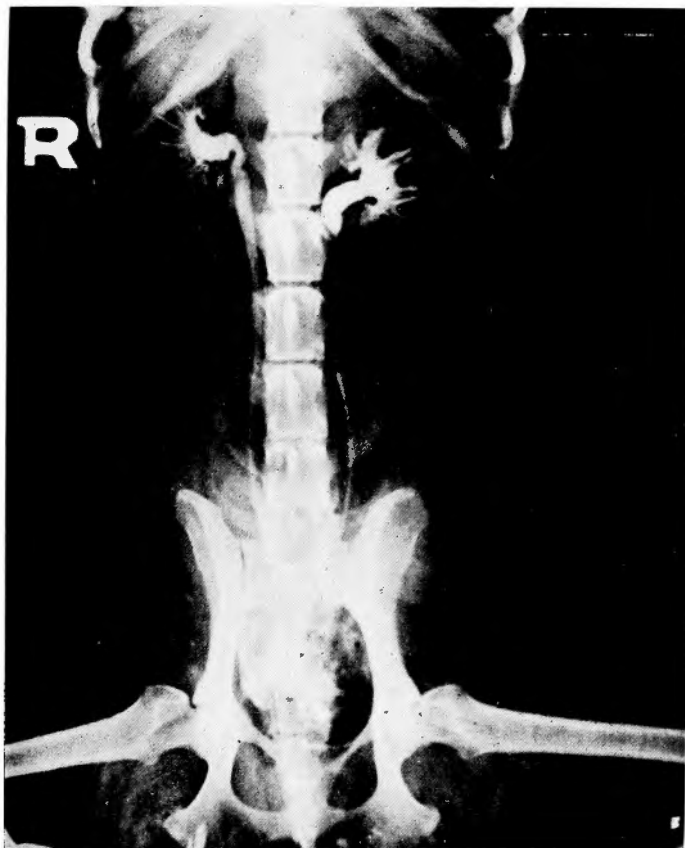


Fig. 10 Retrograde Urogram: Before the Removal of the Polyvinyl Formal Mold.



Fig. 11 Retrograde Urogram: On 30th Postoperative Day (on 11th Day after the Removal of the Mold). Reflux is noted.

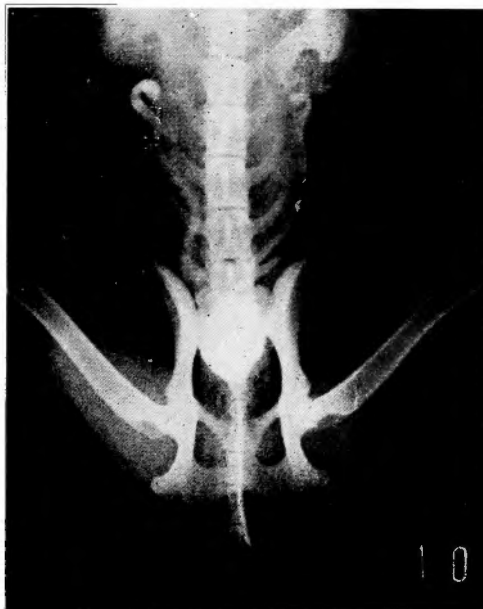


Fig. 12 Retrograde Urogram: In 6th Postoperative Month. Capacity 32cc.

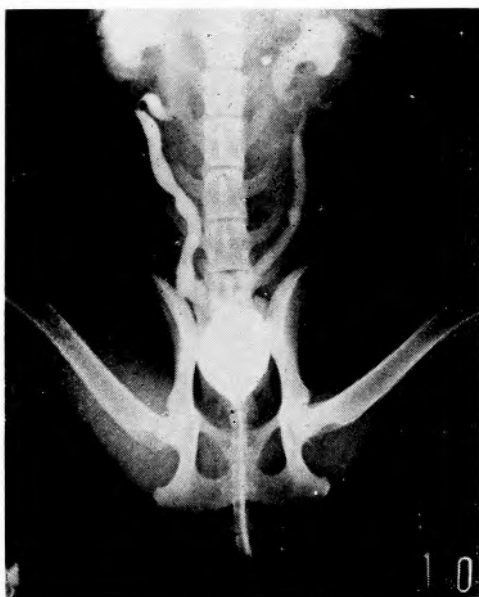


Fig. 13 Retrograde Urogram: In 10th Postoperative Month. Capacity 42cc. Reflux and dilatation of the upper urinary tract are noted.

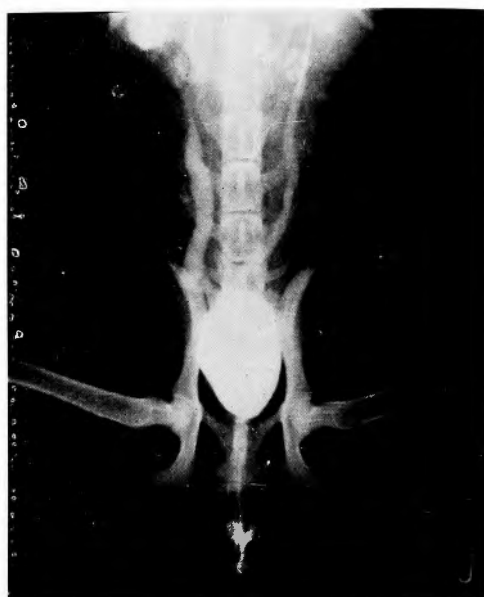


Fig. 14 Retrograde Urogram: In 12th Postoperative Month. Capacity 45cc.

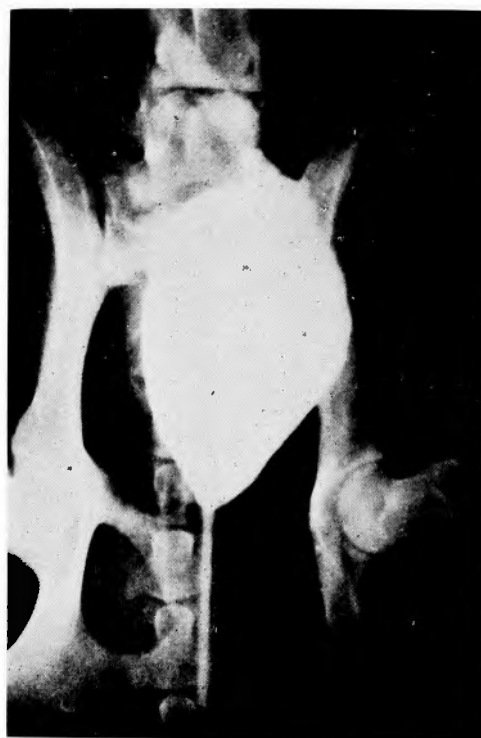


Fig. 15 Cystogram: In 12th Postoperative Month (Antero-Posterior View).

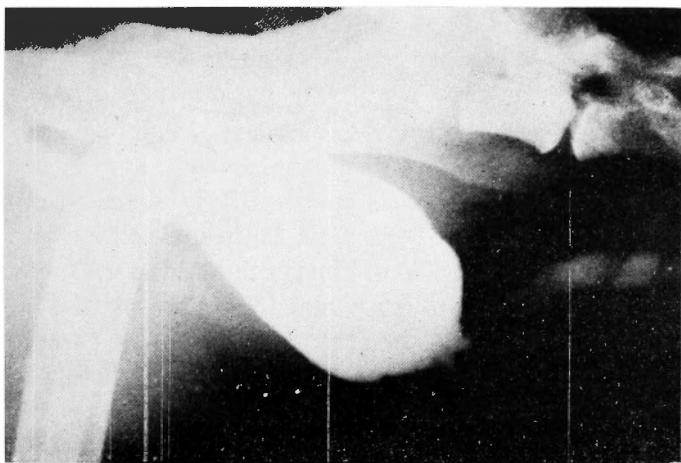


Fig. 16 Cystogram: In 12th Postoperative Month (Lateral View).

Autopsy Findings: It was about 3.0 cm from the opening end of the fistula to the posterior wall of the regenerated bladder. Formation of the pouch was comparatively good. Its wall was 0.5 cm in thickness and its inside was smooth, but not glossy. The junction between the urethra and the pouch was comparatively distinguishable and there was no proliferation of the uroepithelium. The capacity of the pouch was 17 cc and smaller than the volume of the mold. The right ureteral orifice was occluded owing to marked proliferation of the connective tissue, and the left ureteral orifice also showed moderate stenosis. There was moderate hydronephrosis on the right side, and pyohydronephrosis on the left side. On 10th postoperative day, blood chloride and nonprotein nitrogen showed temporal decrease, but since then, began to increase gradually, and showed marked elevation after the removal of the mold, maintaining the rising inclination till the dog died.

Case 3. Dog: No. 34. Weight: 12.7 kg. Period of Survival: 15 days. Cause of Death: Panperitonitis. After total cystectomy, a 20 cc polyvinyl formal mold was indwelt. On 3rd postoperative day, the dog recovered from surgery; urine was continuously dribbling from the ureteral catheters, and the perineum was contaminated with urine. Till about 10th postoperative day, her urination was good and she squatted at intervals of 3 to 5 minutes. On 15th postoperative day, she died of general emaciation and anorexia.

Autopsy revealed that the direct cause of death was panperitonitis due to insufficient anastomosis of the anterior wall of the pouch. Formation of the pouch was incomplete, and its wall suffered generally from inflammatory affection and was 0.4 cm in thickness and its inside was rough, with slime on the surface. There was stenosis at both ureteral orifices, and both kidneys had slight sign of hydronephrosis. The capacity of the pouch was 15 cc showing contraction due to cicatrization.

Case 4. Dog: No. 35. Weight: 8.0 kg. Duration of Survival: 35 days. Cause of Death: Pyohydronephrosis. After total cystectomy, a 13 cc polyvinyl formal mold was inserted and indwelt. The dog recovered from surgery on 2nd postoperative day. Excretion of urine was noticed dribbling from ureteral catheters, and

she squatted at intervals of 3 to 5 minutes. This condition continued till 14th postoperative day, and on 15th postoperative day, the mold was removed. The anterior wall of the pouch adhered slightly to parietal peritoneum and the posterior wall firmly to the uterus and the uterine ligament. The wall of the pouch was 0.8 to 1.0 cm in thickness, and its inside was smooth and glossy. The junction between the urethra and the pouch was comparatively sufficient and was lined with the uroepithelium. There was no stenosis at both ureteral orifices. The urethral catheter was inserted from the inside of the pouch and the wall was sutured serially. The dog recovered from surgery already on the following day after the second operation, with dribbling bloody urine from the urethral catheter; on 2nd day urine was dribbling from both orifices of the urethra and fistula, and it was not mixed with blood. This urinary fistula existed for three days, being closed spontaneously. From about 30th postoperative day, her general condition worsened and she died on 36th postoperative day.

Autopsy revealed that the direct cause of death was pyohydronephrosis on both sides. The capacity of the pouch was 10 cc, showing contraction. The wall was 0.8 to 1.0 cm in thickness and its inside was smooth and glossy; and the junction between the urethra and the pouch was indistinguishable. The uroepithelium developed from the urethra and had covered about one third of the pouch. The right ureteral orifice had marked stenosis. Blood chloride and nonprotein nitrogen increased postoperatively on account of surgery, but they began to decrease from about 11th postoperative day; and after removal of the mold, they showed marked elevation. Phenolsulfophthalein was 21%, but after the mold was removed, it became 12% and, showed a remarkably low value of 10% just before her death.

Case 5. Dog: No. 36. Weight: 11.4 kg. Period of Survival: 7 days. Cause of Death: Urinary leakage. After total cystectomy, a 20 cc polyvinyl formal mold was used. The dog recovered from surgery on 2nd postoperative day, and her urination was good. On 3rd postoperative day, however, she pulled out the urethro-ureteral catheters, and as the result she fell into general emaciation and died of urinary leakage on 7th postoperative day.

Autopsy Findings: Bloody urine stagnated in the abdominal cavity, and formation of the pouch was incomplete. The wall of the pouch was 0.6 to 0.8 cm in thickness and its inside was rough and had no gloss. The urethra and the pouch were not completely united yet, but there was noticed no insufficiency of anastomosis. There was no development of the uroepithelium. The right stump of the ureter showed an insufficient anastomosis, and urinary leakage was noticed through the anastomosis. Hydroureter on the left side was moderate, but slighter than that on the right side. The right kidney had moderate hydronephrosis.

Case 6. Dog: No. 37. Weight: 7.5 kg. Period of Survival: 21 days. Cause of Death: Panperitonitis. After total cystectomy, a 20 cc polyvinyl formal mold was used. The dog recovered from surgery on 2nd postoperative day; urine was voided in dribbling from both ureteral catheters and she squatted at intervals of 3 to 5 minutes. This condition continued till the mold was removed on 14th postoperative

day, when the pouch was already established perfectly. The anterior wall of the pouch moderately adhered to the parietal peritoneum, and the posterior wall to the uterus and the uterine ligament. The wall of the pouch was about 0.8 cm in thickness and its inside was smooth, but covered with slime here and there on its surface. The junction between the urethra and the pouch was favorable, but there was only a slight development of the uroepithelium. Ureteral orifices showed no stenosis and it was possible to see the orifices directly, from which urinary flow was noticed. A urethral catheter was inserted from the inside of the pouch and the wall was closed serially. On 15th postoperative day, a urinary fistula had been formed, but a great amount of urine was voided in dribbling from the urethral catheter. This fistula existed for four days and was closed spontaneously. From about this time, symptoms of panperitonitis was noticed, and she died of general emaciation on 21st postoperative day.

Autopsy revealed that the direct cause of death was panperitonitis, especially developed from inflammatory pouch. The capacity of the pouch was 18 cc, showing contraction. The wall was 0.5 to 1.0 cm in thickness and its inside was smooth but not glossy. The junction between the urethra and the pouch was favorable, and development of the uroepithelium was poor. Both ureteral orifices showed moderate stenosis, and both kidneys presented a picture of moderate pyohydronephrosis, and swelled to be 1.5 times as large as the normal size. Blood chloride and nonprotein nitrogen were elevated temporarily, but decreased to their normal value just before the mold was removed. After the removal, they showed sharp elevation, which was caused by panperitonitis and pyohydronephrosis. Phenolsulfophthalein test showed also the same change.

Case 7. Dog: No. 38. Weight: 14.0 kg. Period of Survival: 120 days. Cause of Death: Sacrificed. After total cystectomy, a 15 cc polyvinyl formal mold was indwelt. On 3rd postoperative day, the dog became well; urine was continuously dribbling from the ureteral catheters, and she squatted at intervals of 3 to 5 minutes. On 30th postoperative day, the mold was removed. The anterior wall of the pouch adhered slightly to the parietal peritoneum and, its posterior wall, to the uterus. The wall was 0.8 to 1.0 cm in thickness and its inside was smooth and glossy. Anastomosis of the urethra and the pouch was perfectly smooth, one third of the pouch being covered with the proliferated uroepithelium, and that of the pouch to the ureters was also sufficient. A urethral catheter was inserted into the internal urethral orifice, and its end was pulled out of the external urethral orifice and fixed to the greater labium. On 2nd day after the second operation, there was formed a urinary fistula in the suprapubic wound, to exist for two days, but be closed spontaneously. On 6th day after the second operation, the urethral catheter was removed. Phenolsulfophthalein test showed 18%, blood chloride 386 mg/dl, and nonprotein nitrogen 52.7 mg/dl; that is, there was renal disfunction. Determination of urinary quantity on 40th postoperative day, revealed that her urination was incontinent all through 24 hours. On 65th postoperative day, the dog recovered to the normal condition; that is, blood chloride was 410 mg/dl, and nonprotein

nitrogen, 33.7 mg/dl. Phenolsulfophthalein test showed, however, 24%, indicating moderate hypofunction. On 70th postoperative day, ascending cystogram showed marked ureteral reflux; the capacity of the bladder was 10 cc, showing its contraction. On 73rd postoperative day, relative continence was noted. On 95th postoperative day, she had yet continence, which was proved by determination of urinary quantity and by the fact that her perineum was not contaminated. On 120th postoperative day, the dog died of excess-anesthetizing for cystometric examination.

Autopsy Findings (Fig. 19): The anterior wall of the pouch adhered to the parietal peritoneum and the posterior wall, to the uterus. The pouch contracted owing to cicatrization and its capacity was 10 cc and smaller than the mold. Its inside was smooth and glossy, with the uroepithelium developed all over the surface. And smooth muscle fibers were noticed to have grown in the wall, which was 0.8 to 1.0 cm in thickness. The pouch was strictured at the junction with the urethra and near ureteral orifices. There was ossification around these orifices; and in the pouch a cystolith had been formed, making suture thread as its nucleus. Ureters showed marked dilatation, that is, hydroureter and hydronephrosis were especially marked on the left side. Blood chloride and nonprotein nitrogen showed temporal elevation after the first and the second operation, respectively; but they showed gradual decrease, and got near to the normal level, which continued till she died. The curve of phenolsulfophthalein test showed also the same inclination, but it always revealed the existence of moderate hypofunction of the kidneys.

Case 8. Dog: No. 39. Weight: 9.7 kg. Period of Survival: 31 days. Cause of Death: Pyohydronephrosis. After total cystectomy, a 20 cc polyvinyl formal mold was used. As the dog began to show general emaciation, the mold was removed on 10th postoperative day. Formation of the pouch was comparatively good, and its wall was 0.6 cm in thickness, its inside being smooth, with slime on the surface. The junction between the urethra and the pouch was still distinguishable, without any proliferation of the uroepithelium. Urinary flow from both ureteral orifices was noted. Uretero-urethral catheters were inserted, and the wall was closed. There was noted no formation of urinary fistula, and urination from ureteral catheters was good; but the perineum was contaminated with urine. Uretero-urethral catheters were removed on 8th day after the second operation, when the lumen of ureteral catheters was partially occluded with urinary elements. She became emaciated from about 29th postoperative day, and died on 31st day.

Autopsy Findings: The wall of the pouch was 0.8 to 1.0 cm in thickness, and its inside was smooth. The pouch contracted to 12 cc, being smaller than the mold. The junction between the urethra and the pouch was rather indistinguishable, and proliferation of the uroepithelium was noticed only at the site of anastomosis. Both ureteral orifices showed marked stenosis, owing to proliferation of connective tissue. Both kidneys showed hydroureter and pyohydronephrosis. Blood chloride and non-protein nitrogen were normal before the removal of the mold, but showed a moderate elevation thereafter.

Case. 9. Dog: No. 40. Weight: 10.0 kg. Period of Survival: 60 days. Cause

of Death: Hydronephrosis. After total cystectomy, a 25 cc polyvinyl formal mold was inserted. The dog recovered from surgery on 3rd postoperative day. When the mold was removed on 27th postoperative day, the wall was 0.8 to 1.0 cm in thickness, and its inside was smooth and glossy. The junction between the urethra and the pouch was indistinguishable and the uroepithelium was proliferating into the pouch. Ureteral orifices showed no stenosis, from which urine was flowing out. After the removal of the mold, uretero-urethral catheter was inserted. There was no formation of urinary fistula after the second operation; and on 33rd postoperative day, the catheter was removed. On 35th postoperative day, her urination was still incontinent, but she squatted intermittently, voiding about 5 cc of urine each time. Cystometric examination on 40th postoperative day revealed that the highest value was 9.5 cm H₂O, that is, infusion of 32 cc caused overflowing. She became emaciated gradually from 55th postoperative day and died on 60th day.

Autopsy Findings: Formation of the pouch was good, and its wall was 0.8 to 1.0 cm with capacity 23 cc, showing slight contraction. The inside was smooth and had a small area of slime on its surface. The uroepithelium developed over one third of the inside of the pouch. Junction between the urethra and the pouch was completely indistinguishable. Both ureteral orifices showed slight stenosis and moderate hydronephrosis. Blood chloride showed temporal elevation postoperatively, indicating gradual decrease subsequently. Nonprotein nitrogen showed marked increase postoperatively, and continued to increase slightly even after the removal of the mold. As for phenolsulfophthalein test, it was 26% on 10th postoperative day, but became 19% after removal of the mold and 14% just before death.

The causes of death, complications and others of the cases mentioned above are shown in the Tables 4 and 5.

Table 4. Polyvinyl Formal Mold Group.

Dog No.	Weight (kg)	Volume of the Mold (cc)	Period of Surviving (day)	Cause of Death	Reference
28	10.5	25	395	Sacrificed	On 19th postoperative day, the mold and the ureteral catheters were removed.
29	9.5	20	18	Pyohydronephrosis	On 13th postoperative day, the mold and the ureteral catheters were removed.
34	12.7	20	15	Panperitonitis	
35	8.0	13	35	Pyohydronephrosis	On 15th postoperative day, the mold and the ureteral catheters were removed.
36	11.4	20	7	Urinary leakage	The ureteral catheters slipped spontaneously.
37	7.5	20	21	Panperitonitis	On 14th postoperative day, the mold and the ureteral catheters were removed.
38	14.0	15	120	Sacrificed	On 30th postoperative day, the mold and the ureteral catheters were removed.
39	9.7	20	31	Pyohydronephrosis	On 10th postoperative day, the mold and the ureteral catheters were removed.
40	10.0	25	60	Hydronephrosis	On 27th postoperative day, the mold and the ureteral catheters were removed.

Table 5. Complications of Polyvinyl Formal Group

Dog No.	Hydro-nephrosis	Pyohydronephrosis	Peritonitis	Urinary Leakage	Urinary Fistula	Slipping of Ureteral Catheters	Angulation of Ureteral Catheters	Stenosis of Ureteral Orifices	Crystallization in Ureteral Catheters	Continence
28	+							+		Yes
29	+	+		+	+			+		No
34	+		+					+		No
35		+		+	+			+		No
36	+		+	+		+		+		No
37		+	+		+			+		No
38	+			+	+			+		Yes
39		+						+	+	No
40	+							+		No

Note : + Slight, + Moderate, + Severe

III. CLINICAL EXPERIENCE

Recently, I have applied the procedure to a patient. I. Kawaguchi, a 59 year-old-Japanese, who had been suffering from a bladder cancer. He was hospitalized on January 11, 1957, because of bloody urine with dehydration. As a papillary cancer was found in the bladder and the rectum, he underwent an operation of total pelvic evisceration, anastomosing the ureters with the external skin on February 23, 1957. The external ureterostomies worked well, and his general condition improved gradually. However, the ureters were frequently obturated by contracting cicatrization, which necessitated temporarily troublesome insertion of a catheter to overcome the condition. Furthermore, the skin around the orifices of ureterostomies was irritated with urine.

Therefore, I decided to perform procedures of bladder regeneration upon him on 7th of May, 1957. The skin incision was made in the median suprapubic line, round the root of the penis, and along the suprapubic white line down to the median raphe of the scrotum. The subcutaneous tissue and the rectus sheath were cut and the peritoneum was exposed. As the patient had a permanent colostomy performed in the previous operation, the peritoneum could not be reflected upward completely, but enough to expose the ureters under direct vision. The right ureter was shorter than the left. Then the author had to go to the next step of the operation to insert a mold in the extraperitoneal space. The polyvinyl formal mold with capacity of 70 cc was covered with the surrounding serous tissue, especially with the peritoneum (Fig. 17). But unfortunately, the peritoneum was not large enough to cover the mold completely because there was so wide defect resulted in by the previous operation, that it was necessary to detect some other materials to cover it, such as rectus sheath, or iliopsoas sheath. Furthermore, the newly constructed extraperitoneal space in which the mold was indwelt was not large enough and was dislocated to the right-side, on account of incomplete peritoneal reflection. With difficult maneuver, I could manage at last to insert the mold into the space. Then, the stumps of both ureters were connected with the mold itself with several fine silk sutures under guidance of the ureteral catheters. The top of the mold could be fixed with the catheters as well as with the above mentioned sutures, but the tail of the mold was difficult to fix. Therefore the urethra could not be connected with the mold

directly, and there was about an inch of gap between them, which was connected by the bridge of the urethral catheter. The superior and the medial side of the mold was covered with the peritoneum, the lateral and the posterior, the iliopsoas muscle, and the anterior, the right rectus sheath.

In spite of the above-mentioned gap, urine was not spilt from the gap but dribbled out through these uretero-urethral catheters. Infection was prevented with some antibiotics, and the wound was closed primarily.

For the time being, the postoperative course of the patient was quite favorable, and he showed no symptoms of unbalance in blood electrolytes. But on 15th postoperative day, the abdominal wall became rigid, showing tenderness. Suddenly, discharge of urine decreased, which indicated acute development of urinary leakage from the gap, and the patient died of panperitonitis against all efforts.

Autopsy was not carried out, but it was supposed that the cause of the leakage might be insufficiency of extraperitonealization.

IV. DISCUSSION

(1) Operative Procedure :

It has been proved experimentally that the regeneration of urinary bladder is possible following total cystectomy. This operation is divided into two stages, the first and the second. The 1st step of the operation is that, after total cystectomy, a resin or a polyvinyl formal mold with ureterourethral catheters is inserted and is covered tightly with the perivesical fatty tissue and the peritoneum. The second step of the operation is that the mold is removed out of the pouch reconstructed around it after 7 or 8 postoperative weeks with suprapubic incision only to insert a urethral catheter into the pouch, which is made to function as a new urinary bladder. Within 4 days to one week after this second operation, the urethral catheter is also removed. What is important in this second stage operation, is to decide the chance to perform it. It is considered to be best that the mold should be removed in 6th to 8th postoperative week. The reason for this is that the connective tissue proliferates always best and formation of a pouch is sufficient in 5th to 6th postoperative week according to my experience, and that the uroepithelium begins to develop in 3 weeks, covering the whole surface of the inside of a pouch in 6 to 8 weeks. If the mold is removed too early, formation of the pouch will be generally imperfect, causing either panperitonitis due to an insufficient anastomosis, or marked ureteral stenosis. If, however, the mold is inserted and indwelt for more than 8 weeks, the ureteral wall will dilate and atrophy of muscle and declination of peristaltic motion will be brought about, so that hydronephrosis will be induced. Judging from these facts, it is concluded that 6th to 8th postoperative week when the uroepithelium develops best and formation of a pouch is finished as mentioned above, will be most suitable for the second operation.

In the first operation, a mold is wrapped up with the peritoneum and the perivesical fatty tissue. This procedure of extraperitonealization of the mold is most important in the operative procedures. Therefore the peritoneum and the

perivesical fatty tissue should be used sufficiently. If these tissues are not enough to extraperitonealize the mold, it may be also possible to use free fascial graft out of the anterior rectus sheath. The necessity of sufficient extraperitonealization should be emphasized.

In the resin mold group, pus had sometimes stagnated in the hollow cavity of the mold owing to its permeability, however sufficient this extraperitonealization might have been. It was not desirable because of danger or developing peritonitis. In order to prevent this, a special resin mold with central cloaca was used (Dogs No. 18 and 24), but it did not work so effectively for drainage of the pus as was expected, and after all it was impossible to prevent peritonitis. On the contrary, the polyvinyl formal group had not a danger like this.

There was noticed fistula formation in the operative wound as a complication after removal of the mold. In case of Dog No. 23, a urinary fistula was noticed in the suprapubic region for three days from 1st postoperative day. In case of Dog No. 29, a urinary fistula was formed for four days from 2nd day after removal of the mold (till its death). Dog No. 37 had a urinary fistula for three days from 1st day after removal of the mold. Dog No. 38 showed fistula formation for 2 days from 2nd day after removal of the mold. Thus, the urinary fistula was formed for 2 or 4 days in general, but closed spontaneously.

In order to prevent formation of a urinary fistula which is liable to appear in suprapubic region, drainage through the ureterourethral catheters should be kept constantly.

As for two kinds of mold, a polyvinyl formal mold has following advantages, when compared with a resin mold,

- i) There is no technical difficulty in making it.
- ii) It has no irritation against vital tissue.
- iii) A resin mold has a hollow cavity and is so permeable, that exudation will stagnate in its cavity; this exudation is harmful, for it is infectious. While, on the other hand, a polyvinyl formal mold is spongy and also able to absorb various antibiotic solution before it is used.
- iv) Besides, it is flexible, and has an advantage of being diminished, when it is left in the body for a long time.

(2) Shape of the Mold:

In cases where ureteral catheters were inserted from the dome of a mold, especially into a resin mold, they were liable to cause angulation at the junction between the catheters and the mold; with the intention of preventing the angulation, isolation of ureters was tried extensively, but the result was the same. This was probably because a resin mold was hard and inflexible. On the contrary, when ureteral catheters were inserted from the middle of the posterior wall of a polyvinyl formal mold, there was no angulation noticed. It prevented not only angulation, but also all dangers due to insufficient fixation, because a polyvinyl formal mold has elasticity or flexibility and accordingly suturing thread can be passed through the mold itself for fixing.

(3) Crystallization in the Catheter:

HUFFMAN (1956) reported that when he performed partial ureterectomy for regeneration of the ureters, there was crystallization in the lumen of a polyethylen tube, and it had played a great role in bringing about infection into the urinary tract. HERDMAN (1949) also perceived frequent occurrences of stenosing crystallization, when he used a polyethylen tube as a splint of the ureters of a dog. According to the report of BOHNE (1955), the lumen of this tube was occluded with nonspecific material as well as calcitic precipitation, and the dog died of irreversible change in kidneys. This crystallization consists of phosphoric acid and uric acid. In the present experiments, Dogs No. 14, 20, 21 and 39 had showed this crystallization, which was produced in about a week in case of the earlier ones. Crystallization will occlude ureteral catheters, causing either hydronephrosis or pyohydronephrosis. One of the effective treatments to prevent the crystallization is either to insert a stylet unto ureteral catheters which are brought out of the external ureteral orifices, or to wash them with 1.5% solution of sodium bicarbonate.

(4) Ureteral Stenosis:

One of the most frequent complications among a series of my experiments is ureteral stenosis, which brings about secondarily hydronephrosis or pyonephrosis, and other undesirable phenomena, such as hyperchloremia or acidosis. Therefore, a great care should be taken to find counter-plan against stenosis of ureteral orifices. It may be grouped into two kinds, dynamic and mechanical.

i) In case of stenosis caused by dynamic effect, the ureteral lumen is dilated owing to insertion of the ureteral catheters for too long a time, so that marked atrophy and weakness of the ureteral wall may be resulted secondarily, and subsequently hydroureter and hydronephrosis, owing to the elevation of internal pressure of the renal pelvis. In order to prevent these complications, cares should be taken to remove the ureteral catheters in 3 to 4 weeks.

ii) In case of those which are brought about mechanically, they are usually caused by proliferation of the infected connective tissue at the site where the ureters are transplanted. The proliferation of the connective tissue might interfere the urine passage from the kidneys to the bladder, resulting in hydronephrosis.

Therefore, in the procedures of ureteroenterostomy, such as COFFEY's method, COFFEY-MAYO's method, NESBIT's method, CORDONNIER's method and MATHISEN's method, procedures to prevent stenosis at the site of transplantation of ureters were eagerly studied. After all, however, it is necessary to pay a careful consideration to the primary healing of the anastomosis.

In these two types of stenosis, mechanical one was more frequently. But it may be possible to prevent stenosis by following procedures. Two flaps are made by giving longitudinal incision to the ureteral stump; it is necessary that these flaps should be tightly sutured with the perivesical fatty tissue and the peritoneum. The extra-peritonealization surrounding these flaps alone could prevent the development of stenosis, because then the reconstructed orifices of the ureters are wide.

(5) Reflux:

Ureteral reflux causes secondarily a rise of intravesical pressure. At first ureteral peristalsis compensates it to some extent and accordingly prevents a rise of intrapelvic pressure. But there is a limit in the compensation, and ureteral reflux appears at last, when the ureteral peristalsis is overcome by the gradually rising intravesical pressure. The intrapelvic hyperpressure will cause ischemia of the kidney parenchyma to decrease glomerular filtration. When a rise of intrapelvic pressure is prolonged, obstruction of tubule's endothel is caused to disturb urinary secretion and reabsorption, and acid base equivalence. In these experiments, too, this phenomenon of reflux was noticed through X-Ray examination. This serious reflux might be avoidable by making tunnel of the ureter obliquely through the wall of the pouch. In some of my experiments, though there was proliferation of the connective tissue, urinary passage was not interfered, but there was noticed ureteral reflux. This was probably because the patency of ureteral orifices was maintained by ossification around the ureteral orifices, namely, the ossification worked as a frame. This reflux causes inevitably ascending infection. If the infection spreads into the pouch, the wall changes into inflammatory granulation, which results in destruction of the wall or contraction of the pouch. Besides, development of the uroepithelium is delayed by the infection. The uroepithelium proliferates from the remnant urinary tract in 6 to 10 weeks if the infection does not occur. The vesical infection will spread into the upper urinary tract to cause pyohydronephrosis. Irrigation of the bladder and administration of antibiotics are best for preventing these complications.

(6) Trauma:

In my present experiment, the dogs themselves often caused accidents. For example, some dogs (Dogs No. 10 and 36) pulled out ureteral catheters earlier than the proper time, which caused either insufficiency of the anastomosis, or stenosis at ureteral orifices, and subsequently hydroureter or hydronephrosis. Some dogs licked their operative wounds frequently, and others bit off thread and opened the operative wound, resulting in peritonitis. In one case (Dog No. 20), strangulation of the bowel was noticed. These accidents caused by dogs themselves could be prevented under careful management during the postoperative course. Besides, as an accident caused by management failure, there was perforation of the kidney due to insertion of a ureteral catheter. Such an accident should be prevented by early discovery or by careful guidance especially in the insertion.

(7) On the Transitional Uroepithelium and the Smooth Muscle (Figs. 18, 19 and 20):

Five to six weeks after a mold is indwelt, the pouch is formed with granulation tissue; its inside is lined with the uroepithelium in 6 to 10 weeks to be made smooth and glossy. This uroepithelium can be considered to proliferate from the urethral and the ureteral mucosa. The proliferation of the uroepithelium is rarely mitotic, but mostly amitotic. Once the wall of the pouch is lined with the uroepithelium, there is no danger of contraction by scarring, and stenosis of ureteral orifices can be prevented. In some cases of long survived dogs, the growth of smooth muscle was perceived in the wall of the pouch. STILLING and PFITZNER (1886) tried the

same experiment and proved that the connective tissue developed at first, changing into smooth muscle. JAKINOWITSH (1879) operated on the lung and the stomach of the experimental animals and recognized growth of smooth muscle, when the scars had been established. BUSACHI (1887) reported on regeneration of smooth muscle fibers at the scar of the lung and the stomach. BERRY (1920) showed also increase of muscular cells out of granulation tissue at curettage of the uterus. BAUMGARTEN (1923) in the same way proved development of smooth muscle in the bronchus. According to BOHNE (1955), smooth muscle develops from fibroblasts similar to genetic cells of the vascular system. BERMAN (1954) used a polyethylene tube as a substitute for the esophagus, but regeneration of muscle was impossible, its splint being surrounded with the epithelium and the connective tissue. FRANK, HINMAN, RUDOLF and OPPENHEIMER (1956) reported that cut ureters had demonstrated development of smooth muscle in 4 to 6 weeks and were repaired.

As is mentioned above, there are two opinions concerning the generation of smooth muscle fibers in granulation. One is that development of smooth muscle is due to the increasing ability of the original smooth muscle fibers, and the other is that it is due to metaplasia of connective tissue cells. In the present study, the bundle of the smooth muscle was demonstrated in the regenerated wall. But the origin of appearance of this smooth muscle fibers was not decided. The fibers do not communicate each other, so that the wall of the regenerated bladder has no contractive ability.

(8) On Biochemistry:

A brief description will be tried about blood electrolytes of the dog with the regenerated bladder (Refer to Miss CHIZUKO IWADA for further information.). There are various reports on the cause of hyperchloremic acidosis following uretero-intestinal anastomosis. In my present experiments of the regenerated bladder, the most common cause of the rise of electrolytes was initial hydronephrosis. The hydronephrosis compresses the renal parenchyma, especially glomeruli and blood capillaries, causing ischemia, decrease of urinary filtration and increase of blood chloride and nonprotein nitrogen as the result. One week after insertion of the mold, so-called initial hydronephrosis is apt to be brought about, being complicated with increase of blood chloride and nonprotein nitrogen. As the time lapses postoperatively, the initial hydronephrosis disappears and the blood electrolytes decrease gradually. After the second operation, there appears transitionary edema at ureteral orifices, and blood electrolytes show secondary increase, to be reduced to the normal level in 2 to 3 postoperative months. Instability of electrolytes will be recovered with the accomplishment of lining with the uroepithelium.

(9) On Ossification and Formation of Cystolith:

Notable facts in my present experiments on the regenerated bladder are that ossification was noted under the uroepithelium of the pouch and that cystolith was formed. In cases of Dog No. 28 and 38, autopsy findings revealed the inside of the regenerated bladder had been smooth and lined with the uroepithelium, showing subepithelial formation of the osteoid tissue. This ossification was noticed in the

wall around the newly transplanted ureteral orifices, and demonstrated in the dogs survived more than three months after the operation. NEUHOF (1917) made a defect on vesical mucosa and tried to repair the bladder with free fascial graft; and he noticed osteoid tissue in the part which had been continually contaminated with urine. This fact was confirmed also by PHEMISTER (1923) and KOOTZ (1929).

Osteoid tissue is generally explained to be formed out of mesenchyma. That is, osteoblast is formed of fibroblast which is originated from mesodermal germ. It is considered that there must be something that induces the classification into osteoblast or fibroblast, but this fact has not been explained sufficiently. It may be constant contamination with urine that induces this classification. When this ossification is developed, the surrounding area of ureteral orifices is hardened and fixed to the pouch; but the ureteral orifices themselves can be kept open without contraction or dilatation. On the other hand, there is a disadvantage that elasticity of the bladder wall will be lost and reflux occurs.

Besides, stone formation was noticed in the regenerated bladder. The stone must have been formed secondarily, with some foreign substance as its nucleus. In the present experiment, there was proved formation of cystolith of about $0.6\text{ cm} \times 0.5\text{ cm}$, making thread as its nucleus. This thread may be the one used in suturing the perivesical fatty tissue, or the one used in closing the anterior wall of the pouch at the end of the second stage operation. In order to prevent such stone formation, cares should be taken not to make thread come out into the inside of the pouch, or cut-gut should be used instead of silk thread. In cases of long survived dogs, which showed formation of cystolith, there were always symptoms of dysuria. Therefore it is necessary to pay attention to vesical pain, urination, or bloody urine and to perform periodical cystoscopy, and lithotomy should be done immediately when cystolith is found.

(10) On the Long Survived Dogs:

Dogs of No. 28 and No. 38 in the polyvinyl formal group were long survivals. Some special observations are to be tried on these two cases.

These dogs underwent urinary incontinence respectively on about 70th post-operative day. There were various facts: 1) the wall of the pouch thickened, 2) the capacity of the pouch decreased, 3) the ureters and the renal pelvis dilated markedly, 4) the pouch contracted on account of the smallness of the mold and 5) the ureters were drawn towards the contracting pouch in maldirection, being stric-tured owing to development of ossification. The reason for recovery to continence may be because urethral angulation was brought about on account of the above mentioned development of ossification, thickening of the wall, decreased capacity of the pouch and hydroureter. This fact is a phenomenon quite similar to that which is seen when MARSHAL's method makes pool of urine possible by urethral angulation, in order to prevent incontinence. The urethral angulation may be the very cause of having relative continence even in the dogs without sphincter.

(11) Increase of Vesical Capacity:

It may be on account of hypertrophy, hyperplasia, proliferation of elastic fibers

and pool of urine, that during a certain period (about 6 postoperative months) the capacity of the regenerated bladder increased 18 times as much as that of the mold, as was seen in case of No. 28. It may be, however, because the pouch became invariable owing to ossification and its wall came to be stabilized by development of the uroepithelium, that the vesical capacity never showed any tendency of further increase after that period of time.

V. SUMMARY AND CONCLUSION.

It has been experimentally proved that regeneration of the bladder is possible after total cystectomy by means of insertion of the mold. The application of this procedure was clinically tried furthermore, but unfortunately, the patient died of a complication, peritonitis due to imperfect extraperitonealization.

It was revealed that the wall of the regenerated bladder showed the regeneration of smooth muscle and ossification, but after 8 weeks, its inside was completely covered with the uroepithelium. The dog's urination with this regenerated bladder was continent and was in an ordinary manner. The reconstructed vesical capacity showed increase of 1.8 times as much as the capacity of the mold. The period of the longest survived dog was 395 days, and that it was sacrificed. The most troublesome complication in the present experiment was the contracture of the pouch due to cicatrization. As this contracture is promoted by infection, it is necessary to administer powerful antibiotics for the purpose of checking the contracture as slight as possible. Further investigations are expected in improvement of the mold to perform the operation in one stage after total cystectomy, in the problem of sphincter and in the study on innervation of the regenerated bladder.

In concluding this paper, it is a great pleasure to acknowledge the kind guidance and revision of Prof. YAEMON SHIRAHARA and Assistant Prof. NAOHICO HARADA, my directors to whom I am greatly indebted, and for the kind help on materials, of Prof. CHUZO NAGAISHI, a member of the Tuberculosis Research Institute of Kyoto University. I am also much obliged to Dr. N. SANO, Dr. Y. NARIKAWA, Doctress Ch. IWADA, Dr. K. ODA, Dr. K. FUKUYAMA, Dentist, M. YASUI, and many other associates concerned for their co-operation.

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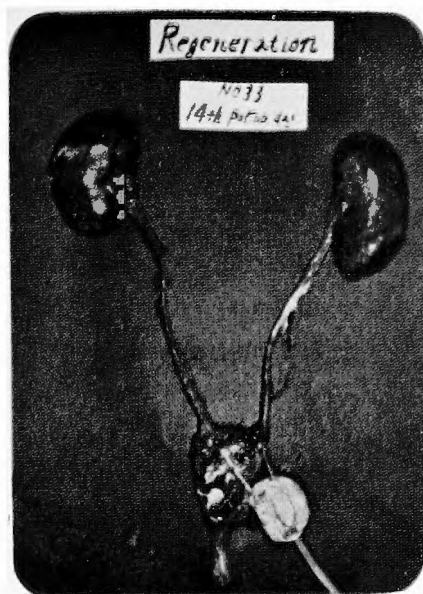


Fig. 1. After total cystectomy, a polyvinyl formal mold with ureteral catheters and a urethral catheter is inserted in to the extraperitoneal space and is covered with the perivesical fatty tissue and the peritoneum.

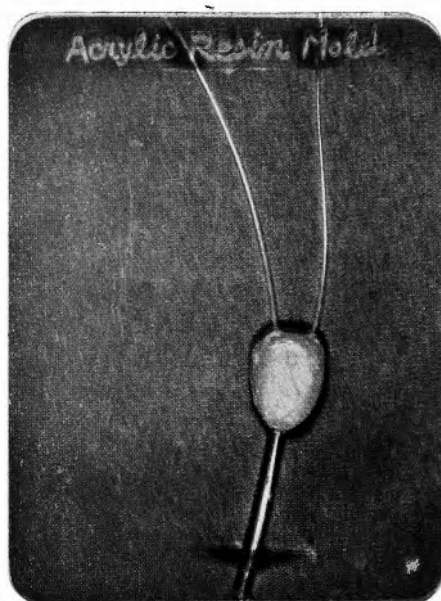


Fig. 2.

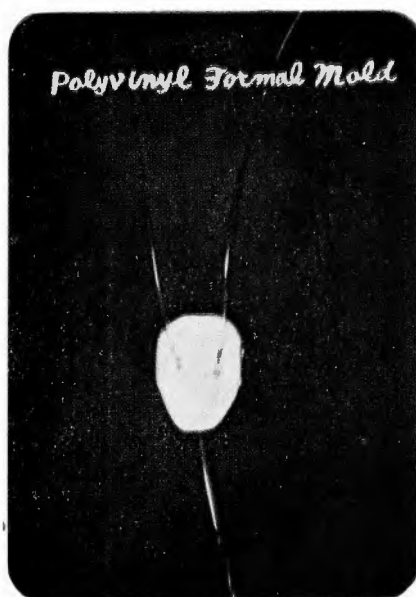


Fig. 3.



Fig. 17. Clinical experience: Median suprapubic incision being performed, a polyvinyl formal mold of 70cc in volume was inserted in the extraperitoneal space. The superior and the medial side of the mold was covered with the peritoneum, the lateral and the posterior, with the iliopsoas muscle, and the anterior, with the right rectus sheath.

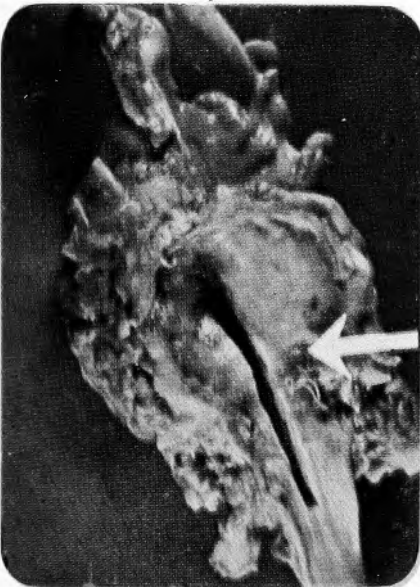


Fig. 19. Autopsy findings on 120th postoperative day: The pouch contracted owing to cicatrization, its capacity being 10cc and smaller than that of the mold. The inside of the regenerated bladder was smooth and glossy, with the uroepithelium developing all over the surface. The wall had 0.8 to 1.0 cm in thickness. There was noted ossification around ureteral orifices, and in the pouch a cystolith had been established.

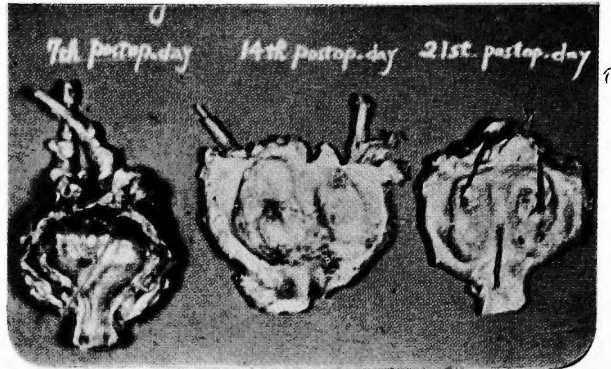


Fig. 18. Autopsy findings on 7th and 14th postoperative days: The wall of the regenerated pouch was 0.5 to 0.8 cm in thickness and its inside was rough, without proliferation of the uroepithelium.

Autopsy findings on 21st postoperative day: The wall of the pouch was about 0.8cm in thickness and its inside was smooth, but there was only a slight development of the uroepithelium.



Fig. 20. Autopsy findings on 395th postoperative day: the capacity of the regenerated bladder was 45 cc, which was 1.8 times as large as that of the mold. The inside of the wall was smooth, lined with the uroepithelium, a calculus of a little finger tip size was noticed in the regenerated bladder, and ossification was recognized in the lower part of the uroepithelium around the ureteral orifices.

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和 文 抄 録

膀胱の再生に関する実験的研究

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膀胱全剔出術後、腹膜外に Mold を設置して、腹膜および膀胱周囲の脂肪組織を用いてその Mold を包埋すれば、膀胱が再生されることを実験的に立証した。

さらに、この方法を臨床的に応用したところ、腹膜による遮断の操作が不十分であつたためか、患者は不幸にも腹膜炎を惹起して死亡した。

一般に再生膀胱壁の内面は Mold 設置後 8 週間後に尿路上皮にて完全に覆われ、その壁の組織中には滑平筋の形成と骨形成とがみとめられた。

再生膀胱をもつ犬は、普通の姿勢で排尿を行なうことができる。膀胱容量は Mold の容積に比較して 1.8 倍の増大を示す。最も長く生存した例は 395 日に屠殺

され、爾後の検索に供された。

今回のわたくしの実験においてみとめられたもつとも重大な合併症は癒痕のために、再生膀胱壁が収縮することであつた。再生膀胱壁の縮小は感染によつて、とくに増強されるので、これを防止するためには、術後における強力な抗生物質の投与が必要であつた。

今後、膀胱全剔出術後ただ 1 回の手術で観血的処置が終了されるように、Mold を改良すること、膀胱括約筋の問題、および再生膀胱の神経支配の問題など、残された諸問題を解明するために、研究を進めなければならない。